REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112 are respectfully requested in light of the remarks which follow.

As correctly indicated in the outstanding Office Action, claims 1-15 are currently pending. Claims 13-15 stand withdrawn as directed to non-elected subject matter. Claim 1 has been amended herein to clarify what Applicants consider to be the claimed invention. Specifically, claim 1 has been amended to recite nonenveloped adenoviruses susceptible to contamination by enveloped viruses, and to clearly recite ranges of values for temperature and pH. Basis for these amendments may be found in the specification and claims as-filed, specifically on page 5, lines 3-22, which discusses the inactivation of enveloped viruses which contaminate a preparation containing nonenveloped viruses, and page 4, line 38 to page 5, line 2, which discuss the degredation of adenoviruses. Thus, this Amendment does not present any new matter. Applicants reserve the right to file a continuation or divisional application directed to any subject matter canceled by way of the present Amendment.

Information Disclosure Statement

Per paragraph 4 of the outstanding Office Action, an English-language abstract of EP 0 812 858 is provided herewith. This reference was filed without an English-language translation in an Information Disclosure Statement on April 17, 2000. Specifically, for clarification purposes, this abstract document discloses a method of inactivating viruses in a FVIII composition using (1) treatment with TNBP solvent and detergent followed by (2) a

heat treatment of the FVIII-containing composition in a freeze-dried state. The method disclosed in EP 812 858 allows inactivation of any virus that are contaminating the protein composition, regardless of the virus nature thus including enveloped as well as non-enveloped viruses, as specifically specified in the attached abstract *"Enveloped and non-enveloped viruses are effectively inactivated"*. Moreover, the inactivation method disclosed in EP 812 858 is a two step procedure which, in addition to the TNBP and detergent treatment, requires high temperature heating (100°C) for a substantial period of time (15-120 mm).

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-12 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. Specifically, the Office Action asserts that the meets and bounds of the present claims are unclear.

It is well established that claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their broadest reasonable interpretation. *In Re Marosi*, 218 U.S.P.Q. 289, 292 (Fed. Cir. 1983). *In re Sneed & Young*, 218, U.S.P.Q. 385, 388 (Fed. Cir. 1983). Applicants submit that when read in light of the specification, the claim language of the present invention must be interpreted to mean that the composition is being manipulated in such a way that enveloped viruses that are contaminating a non-enveloped virus preparation are inactivated while preserving the integrity of the therapeutic non enveloped viruses. This is clearly discussed on page 5 of the present specification as-filed. Nevertheless, in the interest of expediting

prosecution, Applicants amend claim 1 herein to recite a method of inactivating enveloped viruses in a viral preparation comprising non enveloped viruses susceptible contamination by enveloped viruses. Thus, Applicants submit that this rejection is obviated.

Moreover, the Office Action further asserts that the claims are indefinite for the recitation of "about". Applicants submit that the recitation of "about" does not necessarily render the claims indefinite. *Ex parte Eastwood*, 163 USPQ 316 (Bd. App. 1968). In addition, independent claim 1 has been amended herein to clearly recite ranges for the pH and temperature. For example, claim 1 now recites "a pH of about 5 to about 9" to clarify that Applicants intend this claim to recite ranges. Further, the specification as-filed discusses the temperature and pH of the claimed ranges, on page 5, lines 23-34 and page 10, lines 20-34.

Applicants submit that the scope of the claim would be clear to the skilled artisan. Thus, Applicants request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1-12 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Kameyama *et al.* (EP 378 208).

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

> [W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the

> claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the reference cited does not suggest the methods claimed, let alone that the claimed methods could be conducted with a reasonable expectation of success.

Kameyama *et al.* purportedly disclose a method for inactivating viruses that are contaminating a protein composition. More specifically, example 1 of Kameyama *et al.* illustrates treatment with 0.3% of TNBP and 1% of Tween 80 of blood-derived protein preparations contaminated with both enveloped (VSV and Sindbis) and non enveloped (Echo) viruses. After incubation at 30°C, time course sampling was conducted to determine the residual activity of the contaminating viruses. In every preparation, VSV and Sinbis viruses were inactivated after a 1 hour period of time, whereas activity of non enveloped Echo viruses was detectable even after 60 hours of TNBP-Tween 80 treatment at 30°C.

Although the cited reference does not teach the inactivation of enveloped viruses in a non-enveloped viral preparation, in order to further distinguish the present invention from Kameyama, Applicants herein have amended claim 1 to recite a method of inactivating enveloped viruses contaminating a viral preparation comprising adenoviruses.

Applicants further note the following in distinguishing the claimed invention from the cited reference. As disclosed in the Encyclopedia of Virology (copy enclosed herewith), Echo viruses are small envelopeless RNA viruses are members of the Enterovirus genus (of the Picornaviridae family). Their capsid is formed by 60 copies of four non-glycosylated proteins (VP1, VP2, VP3 and VP4) surrounding an 8kb single-strand RNA genome. Little is known about the course of natural infection but Echo viruses infection appears controlled in a species and tissue-specific manner. Due to its relative acid stability, they multiply through the alimentary tract, (see page 357). Entereoviruses are extremely stable. They display acid stability permitting them to survive transit through the stomach. Moreover, they are resistant to degradation mediated by a certain number of chemotherapeutic and chemical agents, as mentioned in Chapter 21 of Virology (1990, 2nd Ed; ed Fields *et al.*, Raven Press; copy enclosed herewith)

In contract, as disclosed in the present invention, adenoviruses are icosaedral virions enclosing a linear double-stranded DNA genome of 36 kb in a protein capsid. The enclosed Figure (from *Adenoviruses Molecular Biology*; Academic Press Limited) illustrates the extreme complexity of an adenoviral particle. The outer capsid is composed of 252 capsomers arranged geometrically to form 240 hexons and 12 penton bases, the latter are located at each vertex from which protude the antenna-like fiber. Adenoviruses can infect almost any cell type, but infectivity depends on the integrity of the viral particles. In this regard, the fiber and penton base present at the surface of the adenoviral particles plays a critical role in the infection and internalization process. The adenovirus enters in cells via interaction of the trimeric fiber with one or more cellular receptor(s). The

particles are then internalized by endocytosis through the binding of the penton base to the cellular αvβ integrin. Thus, the morphology and mechanisms of infection and internalization are totally different between both Echo viruses and adenoviruses and it is likely that the conditions that limit the inactivation of Echo virus are different that the ones that limit inactivation of an adenovirus (for which integrity of the fiber and penton base is essential).

Therefore, the teaching of Kameyama relating to Echo virus-containing preparation can not be broadened to an adenovirus-containing preparation. If the skilled artisan attempted to alter the adenoviral capsid of the present invention during the TNBP-Tween 80 treatment as recited in Kameyama, the virus would be unable to attach and penetrate into the target cells, and thus provide the expression of the therapeutic gene. Applicants draw the attention of the Examiner to Huygues *et al.* ((1995), *Human Gene Ther.* 6: 1403-1416) which reports that adenoviruses are large (diameter of approximately 80 nm) and somewhat fragile (see first sentence, second paragraph on page 1404). In this regard, degradation of adenovirus infectivity is observed upon exposure to a temperature greater than 37°C, as discussed on page 4, line 38 to page 5, line 2 of the specification of the present invention. The fragility of adenoviruses is also supported by the loss of adenovirus activity observed when purifying by means of size exclusion chromatography and hydrophobic interaction chromatography, showing that adenovirus is sensitive to degradation as a result of changes in ionic environment and in the pH of the elution buffer (see page 1408 of Huygues *et al.*).

The specification of the present invention illustrates that TNBP-Tween 80 treatment results in the rapid degradation of the enveloped viruses and the preservation of adenovirus

integrity. Moreover, an increase of the adenovirus titers by a factor 3 or 4 was observed during this inactivation process which is likely due to the action of TNBP solvent on virus aggregates. The observed disintegration of adenovirus aggregates is an unexpected result that is not suggested by the cited prior art.

Thus, in light of what is disclosed in the specification and what was known in the art at the time this invention was filed, Applicants submit that the skilled artisan would have no motivation to attempt the methods of the present invention after reading the cited reference, as there is no expectation of success. Specifically, the disclosure of the cited reference can not be broadened to an adenovirus-containing preparation because this would result in the virus being unable to attach and penetrate into the target cells

Accordingly, Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: October 30, 2002